Hospital admission for hyperemesis gravidarum: a nationwide study of occurrence, reoccurrence and risk factors among 8.2 million pregnancies

Running Title: Hyperemesis gravidarum occurrence and risk factors

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Abstract

Study question: What are the maternal risk factors for hyperemesis gravidarum (HG) hospital admission, readmission and reoccurrence in a following pregnancy?

Summary answer: Young age, less socioeconomically deprived status, nulliparity, Asian or Black ethnicity, female fetus, multiple pregnancy, history of HG in a previous pregnancy, thyroid and parathyroid dysfunction, hypercholesterolemia and type 1 diabetes are all risk factors for HG.

What is known already: Women with Black or Asian ethnicity, of young age, carrying multiple babies or singleton females, with type 1 diabetes or with a history of HG were previously reported to be at higher risk of developing HG; however most evidence is from small studies. Little is known about associations with other comorbidities and there is controversy over other risk factors such as parity. Estimates of HG prevalence vary and there is little understanding of the risks of HG readmission in a current pregnancy and reoccurrence rates in subsequent pregnancies, all of which are needed for planning measures to reduce onset or worsening of the condition.

Study design, size, duration: We performed a population-based cohort study of pregnancies ending in live births and stillbirths using prospectively recorded secondary care records (Hospital Episode Statistics) from England. We analysed those computerized and anonymized clinical records from over 5.3 million women who had one or more pregnancies between 1997 and 2012.

Participants/materials, setting, methods: We obtained 8,215,538 pregnancies from 5,329,101 women of reproductive age, with a total of 186,800 HG admissions occurring during 121,885 pregnancies. Multivariate logistic regression with generalised estimating equations was employed to estimate odds ratios (aOR) to

assess sociodemographic, pregnancy and comorbidity risk factors for HG onset, HG readmission within a pregnancy and reoccurrence in a subsequent pregnancy.

Main results and the role of chance: Being younger, from a less socioeconomically deprived status, of Asian or Black ethnicity, carrying a female fetus or having a multiple pregnancy all significantly increased HG and readmission risk but only ethnicity increased reoccurrence. Comorbidities most strongly associated with HG were parathyroid dysfunction (aOR=3.83, 95% confidence interval 2.28 to 6.44), hypercholesterolemia (aOR=2.54, 1.88 to 3.44), type 1 diabetes (aOR=1.95, 1.82 to 2.09), and thyroid dysfunction (aOR=1.85, 1.74 to 1.96). History of HG was the strongest independent risk factor (aOR=4.74, 4.46 to 5.05). Women with higher parity had a lower risk of HG compared to nulliparous women (aOR=0.90, 0.89 to 0.91), which was not explained by women with HG curtailing further pregnancies.

Limitations, reasons for caution: Although this represents the largest population-based study worldwide on the topic, the results could have been biased by residual and unmeasured confounding considering that some potential important risk factors such as smoking, BMI or prenatal care could not be measured with these data. Underestimation of non-routinely screened comorbidities such as hypercholesterolemia or thyroid dysfunction could also be a cause of selection bias.

Wider implications of the findings: The estimated prevalence of 1.5% from our study was similar to the average prevalence reported in the literature and the representativeness of our data has been validated by comparison to national statistics. Also the prevalence of comorbidities was mostly similar to other studies estimating these in the UK and other developed countries. Women with Black or Asian ethnicity, of young age, carrying multiple babies or singleton females, with type

1 diabetes or with history of HG were confirmed to be at higher risk of HG with an unprecedented higher statistical power. We showed for the first time that socioeconomic status interacts with maternal age, that hypercholesterolemia is a potential risk factor for HG and that carrying multiple females increases risk of hyperemesis compared with multiple males. We also provided robust evidence for the association of parity with HG. Earlier recognition and management of symptoms via gynaecology day-case units or general practitioner services can inform prevention and control of consequent hospital admissions.

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Trial registration number: Not applicable

Keywords: hyperemesis gravidarum, severe nausea and vomiting in pregnancy, pregnancy sickness, hospital admission, risk factors

Introduction

Nausea and vomiting in pregnancy (NVP) is a very common symptom that affects 50-90% of pregnant women and at least a third need clinical intervention (Jarvis and Nelson-Piercy, 2011). The most severe form of NVP, requiring medical treatment, is hyperemesis gravidarum (HG) which affects up to 2% of pregnant women (Poursharif *et al.*, 2007). HG may lead to important maternal conditions such as dehydration, venous thrombosis (Virkus *et al.*, 2014) and depression (McCarthy *et al.*, 2011) and offspring morbidities such as fetal growth restriction and neurodevelopmental delay (Fejzo *et al.*, 2015). Considering these associated risks and the prevalence of HG, which is similar to that of diabetes in pregnancy, it potentially contributes to a significant proportion of currently under-recognised maternal and child morbidity.

The aetiology of HG has been studied but the causes remain unknown and it is extremely difficult to predict in which women clinically important NVP will develop and reoccur in subsequent pregnancies. Different theories suggest that hormonal dysfunction (Verberg *et al.*, 2005), multiple pregnancy (Fell *et al.*, 2006; Roseboom *et al.*, 2011) and a genetic predisposition (Zhang *et al.*, 2011) are all associated risk factors for HG. However most evidence is based on small studies and includes a varied spectrum of severity. In-patient hospital admissions characterised by excessive NVP in 2011 were just under 35,000 for England alone, according to national maternity statistics (Trevelyan Square, 2012). Controversial results have been shown to quantify the extent to which women in the general population will develop HG in first and subsequent pregnancies based on some of their baseline risk factors (Vikanes A, Grjibovski AM, Vangen S and Magnus P., 2008; Y. Fan and H. Jacobsen, 2010).

We assessed over 8 million pregnancies, from hospital records that cover all of England, to quantify the burden of HG and identify important risk factors for HG admission, readmission and reoccurrence in subsequent pregnancies.

Materials and Methods

Study population

The Hospital Episodes Statistics (HES) data contain information on all patients' hospital admissions and outpatient appointments recorded by English secondary care settings within the National Health Service (NHS) hospitals and independent sectors commissioned by the NHS (Health and Social Care Information Centre, 2010). Details of the episode of care include diagnoses defined using International Classification of Diseases version 10 (ICD-10) codes (World Health Organization, 2010) and procedures defined using Office of Population Censuses and Surveys Classification of Interventions and Procedures (OPCS-4) codes (NHS Connecting for Health, 2012). In-patient admissions data have been collected since April 1997 and a subset of these data, known as the HES maternity dataset contains details on all delivery admissions in mothers' records and on all birth admissions for newborns born alive or stillborn. This dataset has been previously validated for perinatal studies (Bragg *et al.*, 2010). We created a cohort of all completed pregnancies by extracting every delivery recorded in the HES maternity dataset where a pregnancy started after 6th April 1997 and the delivery was before 5th April 2012.

Hyperemesis gravidarum definition and severity

All antenatal hospital admissions with an ICD-10 code for HG in the primary diagnosis field were extracted from HES. A pregnancy was considered to be affected by HG if at least one admission with primary diagnosis for HG was recorded during the gestational period excluding the delivery admission. There is no standard measure to assess HG severity and HES does not provide information on intravenous fluids and drug treatments given during admission, so we assessed women's total number of admissions for HG, their total length of hospital stay (in days) and the distribution of admission across pregnancy trimesters.

Risk factors

Risk factors were primarily pre-specified based on associations with NVP or HG previously-reported (Fell *et al.*, 2006; Roseboom *et al.*, 2011) and their availability in HES. Demographic factors extracted directly from patients' admission records were maternal age at the pregnancy outcome, ethnicity and socioeconomic deprivation as measured by the Index of Multiple Deprivation (IMD 2010) in quintiles. The IMD overall ranking is made by combining seven IMD Domain scores (such as income, employment, disability, education) for Lower Layer Super Output Areas (LSOAs) (Department for Communities and Local Government and The Rt Hon Eric Pickles, 2010) which cover approximately 600 households. Hospital admission data were used to assess whether women had a history of HG during a previous pregnancy and the maternal comorbidities, diabetes (pre-existing, gestational and unspecified), hypertension (pre-existing and gestational), hypercholesterolemia, anaemia, thyroid dysfunction and parathyroid dysfunction. Although the association between hypercholesterolemia and NVP or HG has not been studied previously, it is widely

considered as an important complication of pregnancy and was also considered as a suitable proxy for body mass index (BMI), data on which were not available. As the dates of diagnoses are not reported in HES data, we looked at all diagnoses recorded in any admission during the given pregnancy.

The sex of the baby, birth plurality (singleton, twins or other multiple delivery) and parity were obtained from the delivery record in HES maternity data. As parity was incomplete (30% missing) in the delivery record, we additionally used any previously recorded incident deliveries in HES and any diagnostic codes with information on parity. This approach reflects different methods in other work previously published and is in agreement with their final results.(Bragg *et al.*, 2010; Cromwell *et al.*, 2014; Sandall *et al.*, 2014) Such methodology to estimate parity using a look-back technique has been shown to provide accurate estimations of multiparous women but can compromise accuracy of nulliparity (Cromwell *et al.*, 2014). For this reason, we performed a sensitivity analysis restricting the population to women who were from under 20 years of age during the study period to ensure that all their pregnancies were included in the dataset and that the nulliparous rate was as accurate as possible.

Statistical analysis

We calculated the prevalence of HG as a proportion of all pregnancies and assessed variation across all risk factors. We performed logistic regression using a generalised estimating equation (GEE) to account for potential clustering effects from women who had more than one pregnancy during the study period (Hanley *et al.*, 2003). We estimated odds ratios (OR) and 95% confidence intervals (CI) for HG associated with each risk factor, adjusted for maternal age, ethnicity, socioeconomic quintile, parity,

sex of the baby, birth plurality, history of HG in a previous pregnancy, maternal comorbidities, year of delivery, and region of secondary care setting, unless they were the risk factor of interest. Results were presented with 95% confidence intervals to facilitate comparison with prior studies, however in view of the large number of factors (and categorisations thereof) investigated, there was a risk of identifying spurious associations. We therefore used the Benjamini-Hochberg procedure (Benjamini and Hochberg, 1995) to impose a maximum overall false discovery rate (FDR) of 1% for each major outcome (HG, HG readmission and HG recurrence) modelled. Associations where the confidence interval implied significance, but which were rejected under the FDR criterion are highlighted in the results and should be interpreted cautiously. Missing values for any variable were coded and analysed as a separate category.

We described the burden of HG admissions according to the number and length of admissions by trimester (trimester 1 – last menstrual period (LMP) to 13 completed weeks; trimester 2 – start of 14th week to 28 completed weeks; trimester 3 – start of 29th week to delivery) and gestational week (from LMP). We calculated rate of readmission over all pregnancies with HG. We estimated risk of readmission and reoccurrence and assessed which risk factors were associated with each using multivariate logistic regression analysis with a GEE model. For readmission, we compared women with at least one HG readmission to women with no admissions for HG to compare the potentially severe HG cases to the same reference group as the mild HG cases. We assessed reoccurrence of HG amongst women who had HG in their first recorded pregnancy by comparing women with HG in the subsequent pregnancy to women without reoccurrence. We looked for evidence that deprivation might modify the effect of age on each outcome by adding an interaction term

between age group and IMD quintile to the adjusted model. Where the inclusion of this interaction improved the model fit (assessed using Wald tests in the clustered HG and HG readmission outcome models, and likelihood ratio tests in the non-clustered HG reoccurrence model), we used a cell means model to obtain IMD quintile-specific estimates of the effects of age. All statistical analyses were conducted with Stata version 14.

Ethical Approval

All data are anonymised, such that individual patients as well as the name and specific location of residence cannot be identified by researchers. Ethical approval for this study was obtained from The Health & Social Care Information Centre (DSA Reference: NIC-383714-V7G7Q).

Results

There were 8,215,538 pregnancies among 5,329,101 women between 1997 and 2012 of which 0.54% resulted in stillbirths and 1.6% were multiple deliveries. The prevalence of HG in pregnancy was 1.48% with a total of 121,885 pregnancies being affected by at least one primary admission for HG over the study period. Prevalence of admission for HG in pregnancy increased from 1.03% of pregnancies whose delivery occurred in 1998 to 1.75% of pregnancies whose delivery occurred in 2011 and this increase was statistically significant after adjusting for changes in the population's maternal characteristics over time (aOR=1.48, 95%CI=1.43 to 1.53 in 2011 compared to 1998).

Risk factors for hyperemesis gravidarum hospital admissions

Figures for the crude prevalence of HG by maternal characteristics (Table 1) showed that women under the age of 30, with Asian or Black ethnicity and those living in more socioeconomically deprived areas were more likely to be admitted for HG. Multiple pregnancies and female fetal sex were also associated with a significantly increased risk of HG as was history of HG in a previous pregnancy and pre-existing and gestationally developing comorbidities. Adjusted odds ratios for HG in Table 1 show the highest risk of HG in women with Asian and Black ethnicity compared to white ethnicity (aOR=1.82, 95%CI=1.79 to 1.86 and aOR=2.14, 95%CI=2.09 to 2.19 respectively), whereas Chinese women had lower odds of being affected by HG (aOR=0.58, 95%CI=0.52 to 0.66). Female fetal sex and multiple pregnancies interacted to increase HG risk such that singleton females conferred higher odds compared to male singletons (aOR=1.23, 95%CI=1.22 to 1.25) and multiple pregnancies with all female children conferred higher odds of HG (aOR=2.41, 95%CI 2.24 to 2.59) compared to all male children (aOR=2.02, 95%CI 1.86 to 2.18). A history of HG in previous pregnancies was the greatest risk factor for HG in the current pregnancy after adjusting for all other maternal characteristics (aOR=4.74, 95%CI=4.46 to 5.05). Parathyroid dysfunction, hypercholesterolemia and type 1 diabetes were the comorbidities associated with the highest risk of HG with aORs of 3.83 (95%CI=2.28 to 6.44), 2.54 (95%CI=1.88 to 3.44) and 1.95 (95%CI=1.82 to 2.09) respectively, followed by thyroid dysfunction and anaemia. Parous women had a lower risk of HG compared to nulliparous women (aOR=0.90, 95%CI=0.89 to 0.91) and this did not appear to be explained by women with HG having fewer subsequent pregnancies; 44% of them had a second pregnancy compared with 43% of women

without HG. Risk factors generally showed the same patterns of association in nulliparous and parous women (Supp. Table 1, Supp. Figure 1). Restricting the population to pregnancies where women were from under 20 years of age during the study period (3,640,012 pregnancies) showed similar patterns of HG risk in both nulliparous and parous women as found for the whole population.

Hospital readmission for hyperemesis gravidarum

Risk factors associated with readmission for HG (Table 1) showed similar patterns to those for HG admission overall but generally with stronger association especially for history of HG in previous pregnancies, thyroid and parathyroid dysfunctions, hypercholesterolemia, birth plurality and Asian or Black ethnicity.

Maternal age and socio-economic status

In the adjusted analysis we still observed an increased risk of HG and HG readmission among women under 30 years of age compared with those aged 30-34, and a decreased risk in the older age groups up to age 45 (Figure 1). However, in contrast with the figures for the crude prevalence of HG, the increased risks were most pronounced among those in the least deprived socioeconomic groups. The highest risk group overall was those in the least deprived group aged 20-24 years (aOR=1.85, 95%CI=1.76 to 1.96 for HG and aOR=1.71, 95%CI=1.55 to 1.91 for HG readmission). The lowest risk of HG was in women aged 45 or more years from the most deprived group (aOR=0.61, 95%CI=0.43 to 0.87 for HG and aOR=0.51, 95%CI=0.24 to 1.07 for HG readmission). However the risk of HG in those women was nonsignificant according to the 1% FDR criterion and should therefore be interpreted cautiously.

Reoccurrence of hyperemesis gravidarum in a following pregnancy

In the overall population, women affected by HG in one pregnancy and who had a subsequent pregnancy were 33,214 of whom 8,674 had HG in the following pregnancy, accounting for 26% of the risk of HG reoccurrence in a subsequent pregnancy (Table 2); only Asian or Black ethnicity and thyroid dysfunction increased the risk of HG reoccurrence, although the result for thyroid dysfunction was nonsignificant according to the 1% FDR criterion and should therefore be interpreted cautiously.

Burden of hyperemesis gravidarum in England

A total of 186,800 HG admissions occurred during 121,885 pregnancies, the characteristics of which are shown in Table 3. The readmission rate was 28% and within pregnancies with HG, 72% had only one admission, 17% experienced two admissions, whereas 11% had three or more admissions. The vast majority of pregnancies had admissions only in the first trimester (71% of pregnancies with HG), whereas 25% had admissions up to the second trimester and 4% up to the third trimester. Only 10% of pregnancies with admissions for HG were managed as day cases whereas 33% had more than four days of in-patient hospital stay during the pregnancy. HG admissions peaked at eight weeks' gestation (Figure 2) with a median length of hospital stay during the first 18 weeks' gestation of three days (interquartile range(IQR) 2-4) which then decreased to two days (IQR 1-3 days). Of the total admissions, 74% were through an emergency route, 24% were through a maternity ward and only 1% were elective.

Discussion

Main findings

With over 8 million pregnancies, we conducted one of the largest studies internationally to assess the occurrence and reoccurrence of HG and the risk factors for HG hospital admission. Admission for HG has increased over time, occurring in 1.75% of pregnancies where women delivered in 2011 and with a total of 17,629 admissions in 2010 (only for pregnancies ending in live births and stillbirths). Over 28% of women with HG had readmissions within the same pregnancy and the reoccurrence rate in following pregnancies was 26%. This represents a substantial burden on hospitals, which could be reduced or potentially prevented with earlier recognition and management of symptoms in the first trimester via gynaecology day case, midwifery or general practitioner services. We also identified that younger age, less socioeconomically deprived status, Asian or Black ethnicity, a female fetus, multiple pregnancy, nulliparity and several comorbidities are all independent risk factors for HG; these factors could assist in earlier recognition.

Strengths and limitations

We used a rigorous approach in including only records of admission specifying a primary diagnosis of HG, thus excluding a proportion of admissions (3.7%) where HG was reported as secondary diagnosis. Nevertheless, the estimated prevalence of 1.5% from our study was similar to or higher than the average prevalence reported in the literature (Verberg *et al.*, 2005; Vikanes A, Grjibovski AM, Vangen S and Magnus P., 2008; Roseboom *et al.*, 2011; Bolin *et al.*, 2013; Virkus *et al.*, 2014). HG prevalence showed a constant increase over time possibly due to either an

improvement of the coding specificity for HG versus NVP or an increased number of cases presenting to hospital for care and support.

HES data allowed collection of information on the relevant maternal risk factors assessed in this analysis with a fairly low rate of missing values for socio-economic status (0.7%), sex of the baby (3.9%), birth plurality (0.4%) and ethnicity (13.4%). The completeness of birth information in maternity HES has been improving over time (Murray *et al.*, 2012) and the representativeness of our data has been validated by comparison to national statistics (ONS, 2010) and other datasets extracted from HES (Bragg *et al.*, 2010; Sandall *et al.*, 2014). Maternal comorbidities could have been underestimated, missing for instance mild cases of anaemia or diabetes managed in primary care or outpatient secondary care. Nevertheless the prevalence of comorbidities was similar to that in other studies estimating these in the UK and other countries, indicating that women's delivery records capture most relevant comorbidities. We acknowledge that the findings may be affected by residual confounding and unmeasured confounding considering that some potential important risk factors such as smoking, BMI or prenatal care could not be measured with these data. We assessed severity of HG using hospital readmissions, however this may not fully capture severity as readmission in the current pregnancy or reoccurence in a following pregnancy is influenced also by other factors like primary care support, mental attitude and sociocultural factors (McCarthy *et al.*, 2011).

Comparison with previous studies

Younger maternal age, birth plurality (Fell *et al.*, 2006; Roseboom *et al.*, 2011), Black and Asian ethnicity (Vikanes A, Grjibovski AM, Vangen S and Magnus P., 2008), carrying a singleton female baby (Fell *et al.*, 2006; Roseboom *et al.*, 2011), history of HG in previous pregnancies (Zhang *et al.*, 2011) and type 1 diabetes (Fell *et al.*,

2006; Roseboom *et al.*, 2011) were all risk factors for HG, in agreement with previous work. Our large study power additionally enabled us to assess the relationship between birth plurality and fetal sex which showed a higher risk with multiple females compared with multiple males, which supports higher oestrogen levels in the development of HG (Schiff *et al.*, 2004). Among women under 30 years of age, we also found a more pronounced increased risk of HG for those in the least deprived socioeconomic group according to the IMD score, a well validated national measure. These variations could be due to different possible scenarios such as young women from least deprived groups having lower endurance levels to uncomfortable symptoms or older women from most deprived groups being more likely to stay at home for sustaining family needs. A Norwegian study showed that fewer years of education was associated with higher HG prevalence (Vikanes *et al.*, 2013) whereas the opposite was found in an American study (Schiff *et al.*, 2004), although neither were in adjusted analyses. Whilst contrasting results from previous studies (Fell *et al.*, 2006; Louik *et al.*, 2006; Vikanes *et al.*, 2013) and a systematic review (Y. Fan and H. Jacobsen, 2010) showed that the association between HG and parity is not yet well defined, our study showed that nulliparous women had a higher risk of admission for HG compared to parous women, after adjusting for differing maternal characteristics. This was not explained by women with HG curtailing further pregnancies as the proportion of women going on to have subsequent pregnancies was actually similar between women with and without HG in their first pregnancy (44% and 43% respectively). Maternal thyroid dysfunction and anaemia were associated with HG in our study as well as in previous studies (Verberg *et al.*, 2005; Jarvis and Nelson-Piercy, 2011), however the timing of onset of these complications relative to HG is difficult to ascertain in these data.

Hypercholesterolemia had a strong association with HG and to our knowledge no studies have explored this so far. However this result could be affected by selection bias as hypercholesterolemia, as well as thyroid and parathyroid dysfunctions, is not routinely tested for in pregnancy in the UK and thus could have been underdiagnosed in many otherwise healthy women. We found no evidence of association with pre-existing hypertension which was shown in a previous Dutch study, albeit in unadjusted analyses (Roseboom *et al.*, 2011).

Risk for HG reoccurrence was 15% (Trogstad *et al.*, 2005) in a Norwegian study, possibly affected by an underestimation of HG prevalence, and 48% in an American study, likely affected by selection bias (Fejzo *et al.*, 2011). The reoccurrence risk of 26% shown in our study was based on evidence from 33,214 women with HG in their initial pregnancies.

Conclusions

Hyperemesis gravidarum is an extremely debilitating condition that has physical, psychological, social and economic impact on affected women and their families. We have shown that it is responsible for a significant proportion of hospital admissions during pregnancy. However, it is still underestimated by the health professional community resulting in inadequate supportive care for the affected women (Poursharif *et al.*, 2007; Gadsby *et al.*, 2011). This current assessment of HG risk factors in England highlights those women where prediction and possible control of the deterioration of this condition may improve care and reduce admissions (McCarthy *et al.*, 2014).

Unanswered questions and future research

More research is needed to understand the underlying causes of HG including the role of hormonal changes in pregnancy and other pre-existing comorbidities such as

psychiatric conditions. Which type of treatment is effective in reducing admissions and readmission rates and what role prophylactic antiemetic treatments can have are other important unanswered questions. Future studies should also assess the role of out-patient care in the management of HG.

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Authors' roles

LF did the literature search, data management and statistical analyses. All authors contributed to the development of the study design, planned the analyses, and contributed to the interpretation of data. LF and LJT wrote the manuscript with input from all authors and all authors critically reviewed and approved the final manuscript.

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Conflict of interest

CNP reports personal fees from Sanofi Aventis, Warner Chilcott, Leo Pharma, UCB and Falk, outside the submitted work and she is one of the co-developers of the RCOG Green Top Guideline on Hyperemesis Gravidarum; all other authors did not report any potential conflicts of interest.

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Table 1. Risk of hyperemesis gravidarum according to maternal characteristics (N=8,215,538 pregnancies)

Maternal and pregnancy characteristics	Pregnancies in women						Risk of HG		Risk of HG readmission[a]	
	without HG N=8,093,653		with HG N=121,885		with HG readmission N=34,704					
	n	%	n	%	n	%	AOR[b]	95% CI	AOR[b]	95% CI
Maternal age at delivery (years)										
< 20	545,291	*6.74*	9,796	*8.04*	2,410	*6.94*				
20-24	1,515,108	*18.72*	31,619	*25.94*	8,739	*25.18*				
25-29	2,187,967	*27.03*	37,241	*30.55*	11,041	*31.81*	Refer to results from interaction analysis in Fig 1			
30-34	2,334,278	*28.84*	28,590	*23.46*	8,337	*24.02*				
35-39	1,245,589	*15.39*	12,185	*10.00*	3,519	*10.14*				
40-44	252,929	*3.13*	2,322	*1.91*	621	*1.79*				
≥ 45	12,491	*0.15*	130	*0.11*	37	*0.11*				
Socioeconomic quintile										
1 (least deprivation)	1,305,784	*16.13*	13,625	*11.18*	3,722	*10.72*				
2	1,328,418	*16.41*	15,585	*12.79*	4,344	*12.52*				
3	1,461,670	*18.06*	19,817	*16.26*	5,528	*15.93*	Refer to results from interaction analysis in Fig 1			
4	1,728,277	*21.35*	27,506	*22.57*	7,850	*22.62*				
5 (most deprivation)	2,216,406	*27.38*	44,801	*36.76*	13,105	*37.76*				
missing	53,098	*0.66*	551	*0.45*	155	*0.45*				
Ethnicity										
White	5,579,842	*68.94*	74,376	*61.02*	20,111	*57.95*	reference			
Black and white	98,936	*1.22*	2,304	*1.89*	668	*1.92*	1.56	1.49-1.63	1.66	1.53-1.81
Asian	738,389	*9.12*	20,345	*16.69*	6,741	*19.42*	1.82	1.79-1.86	2.12	2.05-2.19
Black	384,520	*4.75*	11,928	*9.79*	3,613	*10.41*	2.14	2.09-2.19	2.33	2.24-2.43
Chinese	41,296	*0.51*	313	*0.26*	85	*0.24*	0.58	0.52-0.66	0.60	0.48-0.76
Other	168,194	*2.08*	2,730	*2.24*	810	*2.33*	1.22	1.17-1.27	1.37	1.27-1.48
missing	1,082,476	*13.37*	9,889	*8.11*	2,676	*7.71*	0.79	0.77-0.81	0.80	0.76-0.83
Birth plurality[c]										
singleton	7,932,988	*98.01*	117,866	*96.70*	33,398	*96.24*	reference			
twins	121,083	*1.50*	3,383	*2.78*	1,111	*3.20*	2.09	2.02-2.16	2.43	2.29-2.59
triplets and more	5,613	*0.07*	163	*0.13*	62	*0.18*	2.33	1.99-2.72	3.17	2.46-4.09
unknown	33,969	*0.42*	473	*0.39*	133	*0.38*	0.97	0.89-1.07	0.95	0.79-1.14
Sex of the baby										
Male	3,868,562	*47.80*	51,899	*42.58*	14,314	*41.25*	reference			
Female	3,814,614	*47.13*	62,459	*51.24*	18,202	*52.45*	1.23	1.22-1.25	1.30	1.27-1.33
not sepcified	8,663	*0.11*	98	*0.08*	30	*0.09*	0.91	0.75-1.12	1.00	0.69-1.45
Multiple males	26,352	*0.33*	657	*0.54*	204	*0.59*	2.02	1.86-2.18	2.26	1.95-2.61
Multiple mixed	34,577	*0.43*	965	*0.79*	325	*0.94*	2.43	2.28-2.60	2.96	2.64-3.31
Multiple females	26,027	*0.32*	774	*0.64*	264	*0.76*	2.41	2.24-2.59	2.98	2.63-3.38
missing	314,858	*3.89*	5,033	*4.13*	1,365	*3.39*	1.17	1.14-1.21	1.15	1.08-1.21
Parity ≥1	3,862,650	*47.72*	59,491	*48.81*	17,116	*49.32*	0.90	0.89-0.91	0.74	0.72-0.75
History of HG	32,353	*0.4*	11,606	*9.52*	5,500	*15.85*	4.74	4.46-5.05	19.58	8.60-20.61
Diabetes[d]										
type 1	29,072	*0.36*	873	*0.72*	248	*0.71*	1.95	1.82-2.09	1.83	1.60-2.09
type 2	8,968	*0.11*	166	*0.14*	50	*0.14*	0.99	0.84-1.16	0.95	0.71-1.28
gestational	122,177	*1.51*	1,944	*1.59*	569	*1.64*	0.95[e]	0.90-0.99	0.92	0.84-1.01
unspecified	17,026	*0.21*	226	*0.19*	76	*0.22*	0.82	0.71-0.93	0.92	0.73-1.17
Hypertension[d]										
pre-existing	28,940	*0.36*	440	*0.36*	120	*0.35*	1.07	0.97-0.18	1.01	0.83-1.22
gestational	239,952	*2.96*	4,068	*3.34*	1,292	*3.72*	1.17	1.13-1.21	1.32	1.24-1.40
unspecified	241,491	*2.98*	4,201	*3.45*	1,196	*3.45*	1.17	1.14-1.21	1.16	1.10-1.24
Anaemia[d]	391,268	*4.83*	8,822	*7.24*	2,800	*8.07*	1.34	1.31-1.37	1.44	1.38-1.50
Thyroid dysfunction[d]	46,619	*0.58*	1,313	*1.08*	483	*1.39*	1.85	1.74-1.96	2.26	2.05-2.50
Parathyroid dysfunction[d]	255	*0.00*	21	*0.02*	10	*0.03*	3.83	2.28-6.44	5.05	2.20-11.61
Hypercholesterolaemia[d]	1,085	*0.01*	52	*0.04*	20	*0.06*	2.54	1.88-3.44	3.05	1.83-5.06

HG=Hyperemesis gravidarum defined by at least one primary diagnosis during a pregnancy hospital admission. 95%CI= 95% confidence interval

[a]Odds ratios for having one or more readmissions for HG in a pregnancy compared with no admissions, according to each risk factor

[b] Odds ratios for HG according to each risk factor adjusted for maternal age, ethnicity, socioeconimic quintile, sex of the baby, year of delivery, region of secondary care setting and all comorbidities, , unless they were the risk factor of interest. An interaction term between maternal age socioeconimic quintile was added to the adjusted model. Reference for parity=nulliparous

[c] For this risk factor a separate model was built excluding sex of the baby from the list of confounders

[d] Diagnosis recorded at any admisson during the current pregnancy

[e] nonsignificant at 1% FDR target (see statistical methods)

Table 2. Risk of reoccurrence of hyperemesis gravidarum in a subsequent pregnancy according to maternal characteristics

Maternal and pregnancy characteristics	Reoccurrence of HG in pregnancy (N=33,214 pregnancies in women with HG in their previous pregnancy)		Adjusted Odds Ratio for reocurrence[a] with 95% confidence interval
	n	*% with reoccurrence*	
Maternal age at delivery (years)			
< 20	1,072	*21.88*	
20-24	2,885	*25.75*	
25-29	2,774	*27.47*	
30-34	1,571	*28.35*	See Fig 1
35-39	346	*25.37*	
40-44	25	*24.04*	
≥ 45	[b]	*n/a*	
Socioeconomic quintile			
1 (least deprivation)	960	*28.39*	
2	1,083	*26.44*	
3	1,384	*26.30*	
4	1,940	*25.95*	See Fig 1
5 (most deprivation)	3,267	*25.41*	
missing	40	*28.37*	
Ethnicity			
White	5,122	*24.73*	reference
Black and white	175	*27.13*	1.19 0.99-1.42
Asian	1,862	*29.67*	1.29 1.21-1.39
Black	1,013	*29.84*	1.33 1.21-1.46
Chinese	18	*18.75*	0.67 0.40-1.12
Other	142	*22.26*	0.88 0.72-1.06
missing	342	*23.51*	0.89 0.79-1.01
Diabetes[c]			
type 1	39	*21.43*	0.75 0.52-1.07
type 2	[b]	*n/a*	0.38 0.11-1.29
gestational	67	*22.87*	0.80 0.61-1.05
unspecified	18	*29.51*	1.10 0.63-1.92
Hypertension[c]			
pre-existing	27	*29.35*	1.19 0.76-1.88
gestational	351	*27.64*	1.08 0.95-1.22
unspecified	308	*24.06*	0.91 0.80-1.04
Anaemia[c]	730	*28.39*	1.09 0.99-1.19
Thyroid dysfunction[c]	79	*33.91*	1.45[d] 1.10-1.90
Parathyroid dysfunction[c]	[b]	*n/a*	1.49 0.27-8.25
Hypercholesterolaemia[c]	[b]	*n/a*	1.40 0.34-5.75

HG= Hyperemesis g ravidarum defined by at least one primary diagnosis during a pregnancy hospital admission

[a] Odds ratios for HG reocurring in pregnancy compared with not reocurring, according to each risk factor adjusted for maternal age, ethnicity, socioeconimic quintile, year of delivery, region of secondary care setting and all comorbidities, unless they were the risk factor of interest. An interaction term between maternal age socioeconimic quintile was added to the adjusted model.

[b] a figure between 1 and 5

[c] Diagnosis recorded at any admisson during the current pregnancy

[d] nonsignificant at 1% FDR target (see statistical methods)

n/a= not applicable

Table 3. Frequency and gestational timing of hyperemesis gravidarum admissions

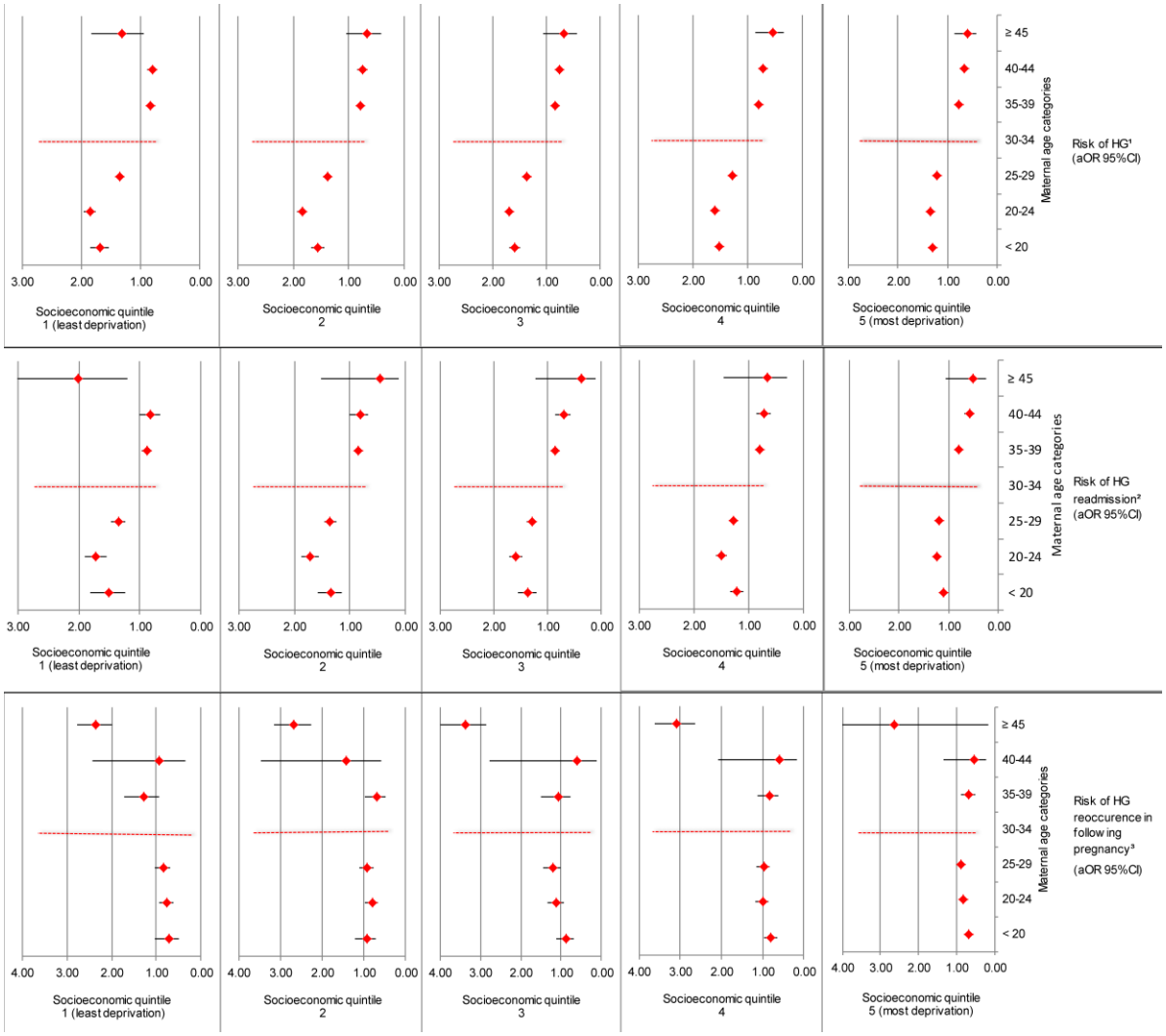
Pregnanices according to admission characteristics		Percentage of pregnancies among women with HG only (N=121,885)	Per 10,000 pregnancies (N=8,215,538)
	n		
Number of admissions per pregnancy: Mean (95% confidence interval)		1.53 (1.53-1.54)	2.27 (2.26-2.29)
Number of admissions per pregnancy			
1	87,181	71.53	106.12
2	20,614	16.91	25.09
3	7,131	5.85	8.68
4	3,253	2.67	3.96
> 4	3,706	3.04	4.51
Trimester of admissions[a]			
first trimester only	85,981	70.54	104.66
up to second trimester	31,065	25.49	37.81
up to third trimester	4,839	3.97	5.89
Admission length (days) in pregnancy			
1	12,919	10.60	15.73
2	28,613	23.48	34.83
3	25,786	21.16	31.39
4	14,057	11.53	17.11
> 4	40,510	33.24	49.31
Admission length (days) in first trimester[b]			
1	69,412	56.95	84.49
2	17,323	14.21	21.09
3	5,651	4.64	6.88
4	2,330	1.91	2.84
> 4	1,744	1.43	2.12
Admission length (days) in second trimester[b]			
1	26,516	21.75	32.28
2	3,430	2.81	4.18
3	981	0.80	1.19
4	448	0.37	0.55
> 4	452	0.37	0.55
Admission length (days) in third trimester[b]			
1	4,391	3.60	5.34
2	330	0.27	0.40
3	76	0.06	0.09
4	22	0.02	0.03
> 4	20	0.02	0.02

HG=Hyperemesis gravidarum defined by at least one primary diagnosis during a pregnancy hospital admission

[a] Pregnancies with admissions in 1st trimester only, 2nd trimester (with or without 1st trimester admissions but no 3rd trimester admissions), 3rd trimester admissions (with or without 1st and 2nd trimester admissions)

[b] Pregnancy may have admissions in more than one trimester so total will exceed total number of pregnancies with HG

Figure 1. Risk of hyperemesis gravidarum (HG), readmission and reoccurrence in a following pregnancy: IMD quintile-specific estimates of the effects of age (aOR= adjusted odds ratio, CI= confidence interval).

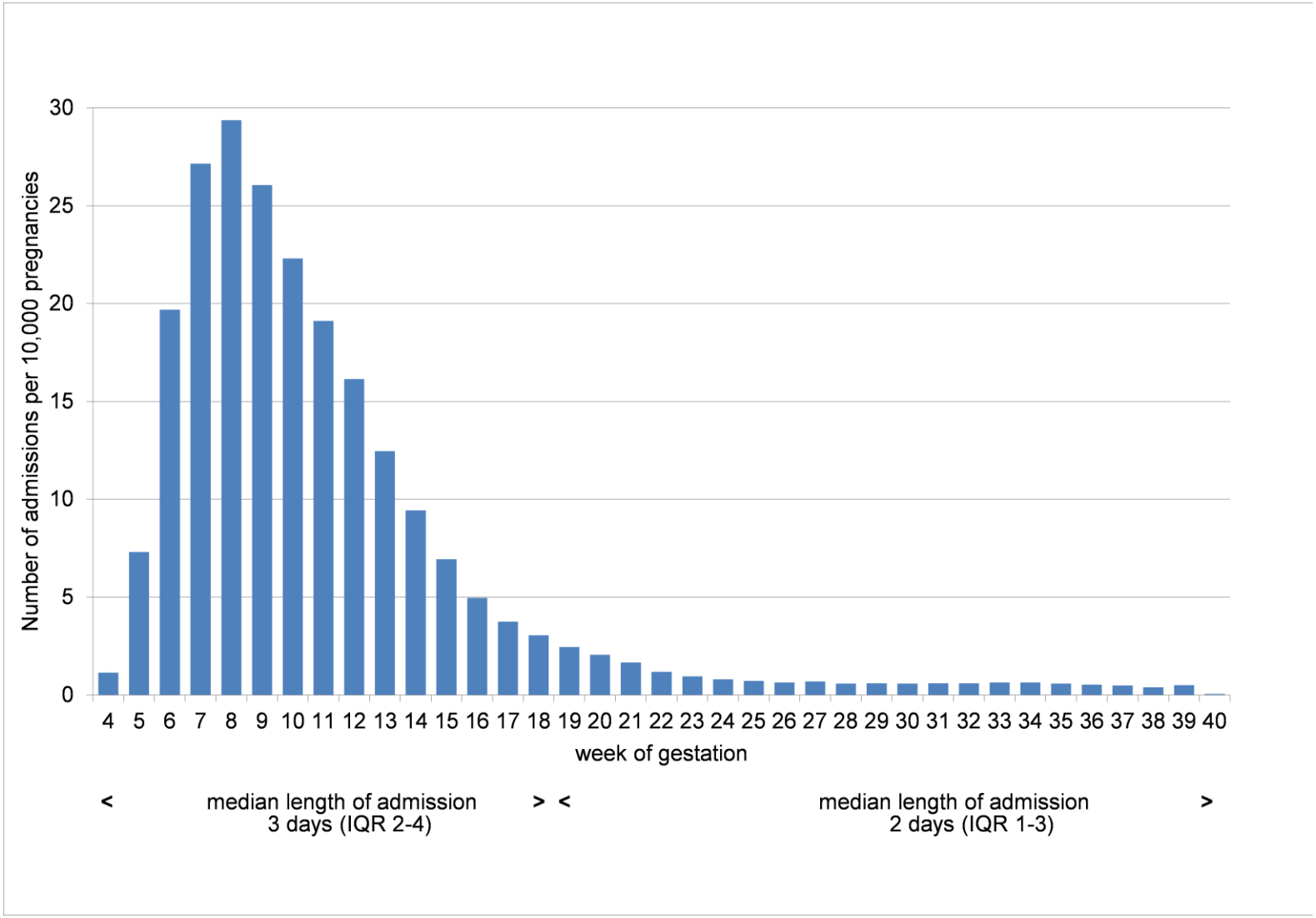


¹ Results for the subgroup of women with age ≥ 45 and socio-economic status 5 are nonsignificant at 1% FDR target (see statistical methods)

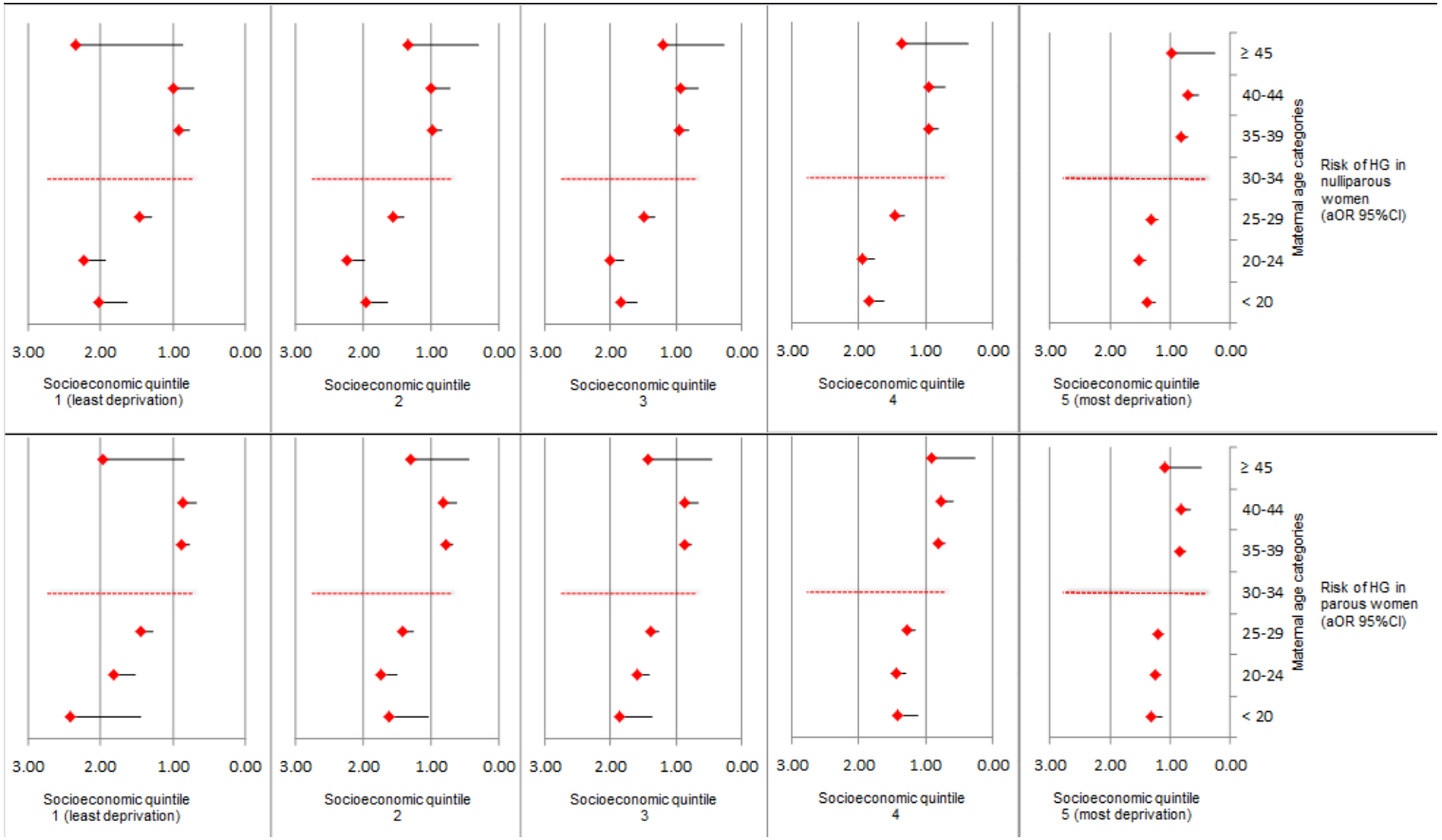
² Results for the subgroup of women with age 35-39 and socio-economic status 1 are nonsignificant at 1% FDR target (see statistical methods)

³ Results for the subgroups of women with age <20 and socio-economic status 4, age 20-24 and socio-economic status 1, 2 or 5, age 25-29 and socio-economic status 3, and age 35-39 and socio-economic status 2 or 5 are nonsignificant at 1% FDR target (see statistical methods)

Figure 2. Admissions for hyperemesis gravidarum by gestational week (IQR=interquartile range)



Supplementary Figure 1: Risk of hyperemesis gravidarum in parous and nulliparous: IMD quintile-specific estimates of the effects of age (aOR= adjusted odds ratio, CI= confidence interval).



Suppl Table 1. Risks of hyperemesis gravidarum in nulliparous and parous women separately (N=8,215,538 pregnancies)

Maternal and pregnancy characteristics	Pregnancies in nulliparous women		Pregnancies in parous women	
	N=4,293,397		N=3,922,141	
	Adjusted Odds Ratios[a] with 95% confidence			
Ethnicity				
White	reference			
Black and white	1.50	1.41-1.60	1.54	1.45-1.63
Asian	1.91	1.87-1.96	1.59	1.55-1.63
Black	2.16	2.09-2.23	1.93	1.87-1.99
Chinese	0.57	0.49-0.66	0.65	0.55-0.77
Other	1.23	1.17-1.30	1.19	1.12-1.27
missing	0.78	0.76-0.80	0.85	0.82-0.88
Birth plurality[b]				
singleton	reference			
twins	2.16	2.06-2.26	2.07	1.96-2.18
triplets and more	2.38	1.94-2.91	2.33	1.80-3.02
unknown	0.96	0.85-1.08	0.97	0.84-1.14
Sex of the baby				
Male	reference			
Female	1.22	1.20-1.24	1.24	1.22-1.27
not sepcified	0.79	0.59-1.04	1.10	0.83-1.47
Multiple males	2.07	1.85-1.31	2.01	1.79-2.26
Multiple mixed	2.55	2.34-2.79	2.36	2.14-2.61
Multiple females	2.43	2.20-2.70	2.45	2.20-2.72
missing	1.19	1.14-1.23	1.14	1.09-1.19
Diabetes[c]				
type 1	2.16	1.96-2.38	1.72	1.56-1.91
type 2	0.94	0.71-1.25	1.03	0.84-1.25
gestational	0.96	0.89-1.04	0.93	0.88-0.99
unspecified	0.89	0.74-1.08	0.74	0.62-0.89
Hypertension[c]				
pre-existing	1.14	0.99-1.30	1.02	0.89-1.17
gestational	1.15	1.10-1.20	1.23	1.17-1.30
unspecified	1.14	1.10-1.19	1.23	1.17-1.29
Anaemia[c]	1.31	1.27-1.35	1.39	1.34-1.44
Thyroid dysfunction[c]	2.10	1.93-2.29	1.65	1.53-1.78
Parathyroid dysfunction[c]	4.61	2.28-9.31	3.17	1.42-7.07
Hypercholesterolaemia[c]	2.71	1.74-4.21	2.56	1.70-3.85

HG=Hyperemesis gravidarum defined by at least one primary diagnosis during a pregnancy hospital admission

[a]Odds ratios for HG according to each risk factor adjusted for maternal age, ethnicity, socioeconimic quintile, sex of the baby, year of delivery, region of secondary care setting and all comorbidities, unless they were the risk factor of interest. Reference for parity=nulliparous

[b] For this risk factor a separate model was built excluding sex of the baby from the list of confounders

[c] Diagnosis recorded at any admisson during the current pregnancy